REMARKS

Applicants respectfully request entry of the amendment, reexamination, and timely notice of allowability.

Initially, applicants request confirmation that the translated French priority document has been received in this application. Applicants filed a certified translation on December 21, 2001.

The composition claims, claims 64 to 75, are all allowable. The Examiner has already indicated that claims 64, 66, and 70-74 were allowed (*see* Office Action Summary for Paper No. 17). The wording in claims 65, 67-69, and 75 has been amended as suggested by the Examiner at pages 5 and 6 of Paper No. 17. Applicants assert that these changes are not necessary for patentability, as one of skill in the art clearly understands and uses the terms "adenovirus" and "cassette" as the terms are used in the claims. However, as the changes do not modify the meaning or scope of the claims, applicants have adopted the Examiner's suggestions to expedite prosecution.

New claims 76 to 128 reflect methods to treat a subject using compositions comprising an adenovirus. All of these claims conform to the format suggested by the Examiner at page 2 of Paper No. 17. There, the Examiner stated that claims for treating a subject, "where said treatment results in an increased lifespan for said subject," are enabled by the specification. The "increased lifespan" language is found in new independent claim 109. As explained in detail below, new independent claims 76 and 77 include additional treatment effects that the specification clearly discloses and enables. As explained in the telephonic interview on November 1st, these method of treating claims are similarly enabled, as they conform to the enabling disclosure of the specification and to that known to be enabled from the specification to one of skill in the art (*see* also page 4 of Paper No. 17, where the Examiner refers to a rejection of the claims to the extent they encompass treatment effects "other than [those] disclosed in the specification"). Here, the new method claims recite a treatment effect specifically disclosed and exemplified in the specification – namely, increased lifespan, the reduction in progressive denervation, and/or the reduction in progressive motor neuron degeneration. Data showing these

treatment results have been included in the Examples of the specification, and some of the specific techniques that can be used as in the Examples are recited in dependent claims 78 and 79.

Claims 76 and 77, in particular, recite "wherein the treatment results in a reduction in progressive denervation" or "progressive motor neuron degeneration" and claim 109 recites "wherein the treatment results in an increased lifespan." These treatment effects are disclosed and enabled by the specification. For example, a clear description of at least two of these treatment effects can be found at page 20, lines 14 through 21 of the English text, reproduced below.

> The results presented in the examples show that the therapeutic approach according to the invention allows the **average length of life** of the *pmn* mice [ALS model] **to be prolonged** to 40 to 53 days, which is a significant improvement of more than 30%. This prolongation of the treated *pmn* mice is also accompanied by a significant reduction of their **motor neuron degeneration**. [emphasis added]

As recognized by the Examiner, the increased lifespan treatment effect and results are clear. Figure 3, and the description of Figure 3 at page 24, line 22, provides additional support for the effect on lifespan. Thus, the increase in lifespan can be demonstrated from an average increase using a model system and/or animals of the same subject animal type.

Furthermore, the quotation above clearly supports the treatment effect on the reduction in motor neuron degeneration. Other parts of the specification put this treatment effect in a more straightforward context. For example, both the $FALS_{G93A}$ and *pmn* mice, noted at page 25, line 19, through page 28, line 25, are shown to be an appropriate model system for studying the degeneration of motor neurons and denervation effects.

In addition, the Examples of this specification employ two techniques, electromyography and observation of the myelinized fibers, which directly correspond to the motor neuron degeneration and denervation treatment effect (as noted in the discussion of the mice model systems). As shown in Example 5, and Figure 4, the claimed treatment results in a "20% reduction in the loss of myelinized fibres" employing the *pmn* mice (page 36, lines 23-25). As one of skill in the art readily recognizes, a loss of myelinized fibers is associated with the

neuronal degeneration of ALS (*see* page 1, lines 14-16 of the specification, for example). Also, as shown in Example 6 and Figure 1, the claimed treatment also effects electromyographic performance.

Example 6 in particular, at page 37, lines 11-20 (reproduced below), puts this treatment effect into perspective.

> The results obtained are presented in Figure 1. A lowering of the amplitude of the motor response evoked (REM) is observed in the gastrocnemius of the treated $FALS_{G93A}$ mice (AdCNTF+AdGDNF) as well as non-treated $FALS_{G93A}$ mice. This lowering reflects the **progressive denervation** process which is characteristic of ALS. Nevertheless, the treated mice show an REM amplitude which is systematically higher than that of the controls, demonstrating a slowing of the functional attack following treatment. [emphasis added]

Similar results are described in Example 7, page 39, lines 12-15 in particular, and in Figure 2. The higher amplitude shown in the graph in Figure 2, for example, for the treated subjects shows that progressive denervation is lower and that the rate of decline of denervation is lower with the treated subjects. Clearly, at least the electromyographic analysis establishes that applicants describe and enable a treatment effect for reducing progressive denervation.

Taken in the context of the specification as a whole, the specific disclosures and examples listed above establish that applicants have enabled and adequately described new claims 76 to 79 and 109, and all the claims dependent upon them.

Applicants note that the language of the dependent claims is taken directly from the prior dependent claims, except that certain non-limiting recitations have been amended as suggested by the Examiner in the rejection under § 112, second paragraph.

For the above reasons, applicants state that no new matter enters by the amendments to the claims and that the new claims are immediately allowable.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 52-63 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to enable one of skill in the art to make and use the claimed invention commensurate in scope with these claims. Applicants respectfully disagree.

The Patent Office premises this rejection on an alleged lack of specific language for a treatment effect in the claims, with the result that the specification allegedly fails to enable an invention commensurate in scope with the claims.

Applicants respectfully state that one of skill in the art would recognize that a method of treating ALS (amyotrophic lateral sclerosis) would necessarily result in some treatment effect if the method was indeed a treatment. Because "treating" is specifically recited in the claims, the requested treatment effect language would be understood by one of skill in the art. Accordingly, applicants' insertion of the functional language into the method of treating claims does not alter the scope of these claims and should not, therefore, be considered an admission that the previous claims were unpatentable.

In the reasons for this rejection (at page 3 of Paper No. 17), the Patent Office states that "the specification does not provide specific guidance for producing a therapeutic effect other than an increase in lifespan, particularly prevention and cure of ALS." Applicants respectfully note that the specification clearly provides specific guidance for a reduction in progressive denervation and a reduction in progressive motor neuron degeneration, as detailed above. Applicants respectfully request reconsideration.

Furthermore, the standard for patent examination purposes should not require or request a cure for disease be demonstrated. As recognized by the Federal Circuit in *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995), the standard for patentability should not relate to the FDA realm of therapeutic effectiveness. The Patent Office must not confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana*, 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995). The Federal Circuit further explained, quoting from the *In re Krimmel* case:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

In re Brana, 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995).

Accordingly, applicants respectfully assert that the claims of the application are indeed enabled by the specification, that applicants have indeed shown a desirable pharmaceutical property, and that a *prima facie* case of lack of enablement has not been made.

Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 53-60, 62, 65, 67-69, and 75 stand rejected under 35 U.S.C. § 112, second paragraph, as the claims are allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Applicants' new and amended claims clarify that the adenovirus vector is used as the nucleic acid that comprises the expression cassette. One of skill in the art would recognize that an adenovirus that comprises an expression cassette could be a vector for expressing a protein or nucleic acid. Applicants have presented claims where the term adenovirus vector is used consistently throughout.

In addition, the expression cassette language has been clarified so that the nucleic acid sequence of the cassette is recited or multiple cassettes are recited. Also, the claims no longer recite "expression cassettes enable simultaneous expression." Applicants note that the simultaneous expression of two separate proteins or nucleic acids is a concept familiar to one of skill in the art, and vectors or combinations for producing this type of expression are known in the art. In a preferred embodiment discussed at page 12, line 9-13 (and the previous pages detailing promoter sequences for such purposes), the specification discloses the use of expression cassettes for simultaneous expression of two nucleic acids.

Finally, applicants have presented claims with the Examiner's suggested language, where the adenovirus vectors "**are**" two replication defective recombinant adenoviruses (Paper No. 17, at page 6).

Applicants respectfully submit that the reasons for this rejection are in error or do not pertain to the present claims.

CONCLUSION

Applicants respectfully submit that this application is in condition for allowance. If the Examiner believes that an interview with applicants' representative, either by telephone or in person, would further prosecution of this application, we would welcome the opportunity for an interview.

No extension of time fees, requests for extension of time, or other petitions, additional claim fees, or other fees are believed to be necessary to enter and consider this paper. If, however, any extensions of time are required or any fees are due in order to enter or consider this paper or enter or consider any paper accompanying this paper, including fees for net addition of claims, applicants hereby request any extensions or petitions necessary and the Commissioner is hereby authorized to charge our Deposit Account No. 50-1129 for any fees. If there is any variance between the fee submitted and any fee required, or if the payment or fee payment information has been misplaced or is somehow insufficient to provide payment, the Commissioner is hereby authorized to charge or credit Deposit Account No. 50-1129.

Respectfully submitted,
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Enclosure(s): Appendix A

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Appendix A: Marked-up version of amended claims 65, 67-69, and 75

65. (amended) The pharmaceutical composition according to claim 64, wherein the vectors comprise an expression cassette sequence for the [enabling] simultaneous expression of two different neurotrophic factors.

67. (amended) The pharmaceutical composition according to claim 66, wherein the adenovirus vectors are [comprise] two replication defective recombinant adenoviruses, and wherein one adenovirus comprises a nucleic acid encoding CNTF and one adenovirus comprises a nucleic acid encoding GDNF.

68. (amended) The pharmaceutical composition according to claim 66, wherein the adenovirus vectors are [comprise] two replication defective recombinant adenoviruses, and wherein one adenovirus comprises a nucleic acid encoding GDNF and one adenovirus comprises a nucleic acid encoding NT3.

69. (amended) The pharmaceutical composition according to claim 66, wherein the adenovirus vectors are [comprise] two replication defective recombinant adenoviruses, and wherein one adenovirus comprises a nucleic acid encoding BDNF and one adenovirus comprises a nucleic acid encoding NT3.

75. (amended) The pharmaceutical composition of claim 64, wherein at least one adenovirus vector is a replication defective recombinant adenovirus vector.